Prospective Cohort Study of Type 2 Diabetes and the Risk of Parkinson's Disease

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OBJECTIVE — To evaluate the association between type 2 diabetes and newly reported Parkinson's disease.

RESEARCH DESIGN AND METHODS — Our study included 21,841 participants in the Physicians' Health Study, a cohort of U.S. male physicians. Diabetes and Parkinson's disease were self-reported via questionnaire. We used time-varying Cox regression to calculate adjusted relative risk (RR) for Parkinson's disease.

RESULTS — Over 23 years, 556 individuals with Parkinson's disease were identified. Subjects with diabetes had an increased Parkinson's disease risk (multivariable-adjusted RR 1.34 [95% CI 1.01–1.77]). The association remained significant after exclusion of those with known vascular disease. The diagnosis of diabetes was clustered around the diagnosis of Parkinson's disease and was more apparent among men with short diabetes duration and those without complications from diabetes.

CONCLUSIONS — Results of this large prospective study in men do not suggest that diabetes is a preceding risk factor for Parkinson's disease. Whether the positive association may be explained by ascertainment bias or a common underlying biological mechanism remains to be established.

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A positive association between diabetes and Parkinson's disease has been found in some epidemiologic studies (1–4) but not in others (5–7). Diabetes might promote Parkinson's disease through various pathways, including suppression of central dopamine levels, inflammation, oxidative stress, and cerebrovascular disease. We evaluated the relationship between type 2 diabetes and Parkinson's disease in detail in a large prospective cohort.

RESEARCH DESIGN AND METHODS

— The Physicians' Health Study is a completed randomized trial of aspirin and β-carotene in the prevention of cardiovascular disease and cancer among 22,071 U.S. male physicians (8). At baseline in 1982, participants were aged 40–84 years and free of major diseases. Health information was self-reported through questionnaires at baseline and during yearly follow-ups. A validation study of the self-report of Parkinson's disease in the Physicians' Health Study found it to be 90% accurate (9).

We excluded participants with Parkinson's disease before study entry, dementia before or within the same year as Parkinson's disease, diabetes before age 25 years, or missing information on diabetes or smoking status, leaving 21,841 individuals for analysis. We used Cox proportional hazards models to estimate the relative risk (RR) of Parkinson's disease. Information on diabetes was updated to incorporate incident case subjects. We adjusted for baseline age, smoking status, alcohol use, BMI, physical activity, and history of hypertension or hypercholesterolemia. We stratified models by baseline smoking status, age, and BMI. We performed sensitivity analyses to determine if diabetes characteristics or known vascular disease (coronary heart disease or stroke) affected the association. We compared the pattern of diabetes diagnosis in Parkinson's disease patients with comorbidity-matched control subjects using a method previously described (9). Diabetes was not included in the comorbidity score. Statistical calculations were performed using SAS (version 9.1; SAS Institute). *P* values are two-tailed; $P < 0.05$ was considered significant.

RESULTS

— Type 2 diabetes was reported by 423 participants at baseline and by 1,987 during the study. Over a median follow-up of 23.1 years (453,954 person-years), 556 participants reported incident Parkinson's disease (median age of diagnosis 73.1 years). Men with diabetes had an increased risk of Parkinson's disease (age- and smoking status–adjusted RR 1.34 [95% CI 1.02–1.77]) compared with nondiabetic men. Further adjustment did not change this risk (1.34 [1.01–1.77]). The association between diabetes and Parkinson's disease was significantly modified by BMI ($P_{interaction} = 0.04$), indicating increased risk for the low BMI group (Table 1). Age and smoking status did not modify this association. Exclusion of patients who developed vascular disease ($n = 5,418$) did not attenuate the risk (adjusted RR 1.46 [95% CI 1.00–2.13]). The highest Parkinson's disease risk was seen in individuals with short-duration, older-onset diabetes without complications. Differences in diabetes incidence between Parkinson's disease patients and matched control subjects was greatest during the year of Parkinson's disease diagnosis and the few years prior (see

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Table 1—*RRs of Parkinson's disease according to history of type 2 diabetes*

	Participants (PD case subjects)		Person-years		RR (95% CI)*		
	Without diabetes	With diabetes	Without diabetes	With diabetes	Without diabetes	With diabetes	$P_{interaction}$
All participants	19,431	2,410	404,923	49,031	1.00 (ref.)	1.34 (1.01–1.77)	
Baseline age (years)							
<55	11,684 (149)	1,247 (12)	259,924	27,489	1.00 (ref.)	1.12 (0.61–2.07)	0.81
55–64	5,140 (194)	790 (26)	103,743	15,937	1.00 (ref.)	1.57 (1.04–2.38)	
≥65	2,607 (155)	373 (20)	41,255	5,605	1.00 (ref.)	1.25 (0.76–2.05)	
BMI							
<25 kg/m^2	11,720 (289)	858 (31)	246,028	17,147	1.00 (ref.)	1.88 (1.28–2.77)	0.04
25 to <30 kg/m^2	7,097 (191)	1,247 (25)	147,109	25,713	1.00 (ref.)	1.14 (0.75–1.72)	
≥30 kg/m^2	614 (18)	305 (2)	11,786	6,171	1.00 (ref.)	0.36 (0.08–1.59)	
Diabetes with complications	19,431 (498)		404,923				
No		1,475 (33)		30,981	1.00 (ref.)	1.63 (1.14–2.33)	0.0002
Yes		935 (25)		18,050	1.00 (ref.)	1.10 (0.74–1.64)	
Diabetes duration (years)	19,432 (498)		404,931				
<5		562 (22)		11,048	1.00 (ref.)	7.17 (4.59–11.20)	<0.0001
5–9		631 (14)		12,945	1.00 (ref.)	2.03 (1.22–3.36)	
10–14		482 (7)		9,921	1.00 (ref.)	0.82 (0.42–1.60)	
≥15		734 (15)		15,109	1.00 (ref.)	0.73 (0.45–1.18)	
Age at onset of diabetes (median)	19,431 (498)		404,923				
≤63.7		1,213 (22)		24,654	1.00 (ref.)	1.18 (0.78–1.79)	<0.0002
>63.7		1,197 (36)		24,377	1.00 (ref.)	1.49 (1.04–2.11)	

Data are *n* (*n*) unless otherwise indicated. *Adjusted for the following baseline variables: age (continuous), smoking status (never, past, or current), alcohol use (rarely, weekly, or daily), BMI (<25 kg/m^2, ≥25 to <30 kg/m^2, or ≥30 kg/m^2), physical activity vigorous enough to work up a sweat (>1–3 times/month or ≤1–3 times/month), hypertension (history of treatment or blood pressure >140 systolic or >90 diastolic), and cholesterol levels (history of treatment or total cholesterol >240). PD, Parkinson's disease.

supplementary Fig. 1*A*, available in an online appendix at http://dx.doi.org/10.2337/dc08-0688). A similar clustering was not seen for the diagnosis of hypercholesterolemia (supplementary Fig. 1*B*).

CONCLUSIONS — In this large prospective study of men, a history of type 2 diabetes was associated with an increased risk of Parkinson's disease. The association remained significant after adjustment for confounders and the exclusion of participants with known vascular disease. If diabetes causes Parkinson's disease, one would expect increased duration and severity to increase Parkinson's disease risk. However, we found the highest risk for Parkinson's disease among individuals with uncomplicated or short-duration diabetes, regardless of baseline age. This was not explained by selective mortality among those with longer diabetes duration (data not shown). Diabetic individuals who developed Parkinson's disease had a longer median time to first complication (17.0 vs. 15.4 years), consistent with decreased severity. Those with a normal BMI at baseline had the highest risk of Parkinson's disease, suggesting a biological pathway other then obesity. Thus, our findings do not suggest that diabetes is a preceding risk factor for Parkinson's disease.

Comparison of Parkinson's disease risk between case and matched control subjects showed that the difference in risk was primarily due to a clustering of diabetes cases around the time of Parkinson's disease identification (supplementary Fig. 1*A*). Thus, one explanation for the association may be detection bias from increased medical surveillance. However, when we examined the diagnosis of hypercholesterolemia, another condition diagnosed by a blood test, we did not observe a similar pattern (supplementary Fig. 1*B*).

Another possible explanation is that the development of Parkinson's disease may influence diabetes risk. By the time Parkinson's disease becomes clinically apparent, dopaminergic cell loss has reached 70–80% (10). Dopaminergic neurons help motivate feeding behavior when glucose levels are low. This feedback loop is mediated by insulin receptors in the *substantia nigra,* and postmortem studies of Parkinson's disease show a loss of these receptors (11). Drugs that modulate central dopamine, such as bromocriptine, are known to affect peripheral glucose control. Changes in glucose control associated with loss of dopaminergic function might occur early in the course of Parkinson's disease, perhaps even before neurological symptoms develop. If Parkinson's disease were a cause of diabetes, one would expect an increased incidence after the diagnosis of Parkinson's disease. However, the incidence dropped dramatically the year after Parkinson's disease diagnosis (supplementary Fig. 1*A*). As over 25% of our Parkinson's disease patients were aged ≥80 years at diagnosis, this might reflect decreased reporting from increased comorbidity and mortality. Parkinson's disease treatment might also modulate diabetes risk.

In conclusion, results of this large prospective study in men do not suggest that diabetes is a preceding risk factor for Parkinson's disease. The observed clustering of diabetes cases around the time of Parkinson's disease diagnosis suggests as-

certainment bias or an underlying common biological mechanism. Future studies are warranted to further unveil this association.

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